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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,795	02/25/2005	Norihito Ohi	0425-1154PUS1	9627

2292 7590 03/29/2007.
BIRCH STEWART KOLASCH & BIRCH
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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/29/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/29/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/509,795	OHI ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,22,23,49-55 and 59-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,22,23,49,53-55 and 59-62* is/are rejected.

7)☒ Claim(s) *50-52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/08/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 20, 22, 23, 49-55 & 59-62 are currently pending in the instant application; of which **Claims 20, 23 & 61** are currently amended and **Claim 62** is new. **Claims 1-19, 21, 24-48 & 56-58** are cancelled.

Information Disclosure Statement

Applicants' information disclosure statement (IDS), filed on 02/08/2007 has been considered. Please refer to Applicants' copy of the 1449 submitted herein.

Response to Amendment

Applicant's amendment, see Amendment – After Non-Final Rejection, filed 12/26/2006, with respect to **Claims 20, 23 & 61** have been fully considered and are entered. The 102 rejections of **Claims 20 & 50-61** and the 101/112 rejections of **Claims 56-58** have been withdrawn per amendment; however, the 112 rejections of **Claims 53-61** and the ODP rejections of **Claims 20, 22, 23 & 50** are maintained. Further, new rejections are presented.

Response to Arguments

Applicant's arguments, filed 12/26/2006, have been fully considered but they are not persuasive. With respect to the enablement rejection made on **Claims 53-61**, Applicant's argue that the field of invention is well developed (the use of compounds having JNK inhibitory effect in the treatment of neurodegeneratory conditions) because

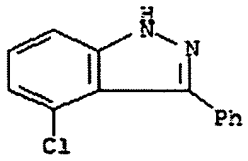
those skilled in the art are aware of the involvement in neurodegeneration. However, a nexus to make this jump in life sciences has not been made. Knowledge of involvement does not translate into an established mechanism of action and an established treatment. For this reason, even with a high level of skill in the art, one would require an undue amount of experimentation in order to use the invention (treat the plethora of diseases) as claimed.

Claim Rejections - 35 USC § 102

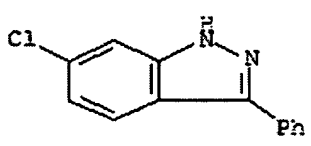
The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20 & 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Simon *et al.* (*Justus Liebigs Annalen der Chemie* **1966**, *697*, 17-41). Shown below are compounds RN 13097-02-4 & RN 13097-04-6, which anticipate formula (III) wherein: **L** = bond; **X** = bond; **Y** = H; $\mathbf{R^1}$ = Ph (**h, j & k** = 0); and at least one of $\mathbf{R^d}$, $\mathbf{R^e}$ & $\mathbf{R^f}$ are not hydrogen (one is halogen).

RN 13097-02-4



RN 13097-04-6



Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 49 recites the limitation "Substituent group a2 described in claim 43". There is insufficient antecedent basis for this limitation in the claim because claim 43 is canceled.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53-55, 59 & 60-62 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for compounds (and compositions) and a method of making these compounds, does not reasonably provide enablement for 1) *preventing* any diseases or disorders; and 2) the treatment of the diseases encompassed within the scope of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'."

In re Wands, 8 USPQ2d 1400 (1988), discusses the following factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph:

1. ***The nature of the invention;***
2. ***The state of the prior art;***
3. ***The predictability or lack thereof in the art;***
4. ***The amount of direction or guidance present;***
5. ***The presence or absence of working examples;***
6. ***The breadth of the claims;***
7. ***The quantity of experimentation needed; and***
8. ***The level of skill in the art***

each of which is discussed in turn below.

The nature of the invention

The nature of the invention of **Claims 53-55, 59 & 60-62** is the use of an agent comprising a compound according to Formula (III) for the treatment and/or prevention of immunological, inflammatory, neurodegenerative, or metabolic diseases.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. *In the instant case,* the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may inhibit JNK and have involvement (either directly or peripherally within the mechanism of action) in assays, but it does not mean that the same group of compounds and compositions may prevent or treat all immunological diseases, inflammatory diseases, neurodegenerative diseases, or metabolic diseases.

To date, there have been four distinct mitogen-activated protein kinases (MAPKs) characterized in mammals: ERK, JNKs, p38 isoforms, and ERK5. **Claims 53-55, 59 & 60-62** are drawn to methods of treating or preventing a disease based on the inhibition of JNK. C-Jun N-terminal kinases (JNKs), are mitogen-activated protein kinases which are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock, and are involved in T cell differentiation and apoptosis. The c-Jun N-terminal of MAPK consists of three isoforms. JNK1 and JNK2 are ubiquitinous distributed, but JNK3 is found mainly in neuronal tissue. All JNKs are activated by the upstream kinase MKK7. JNK has been implicated in conditions including diabetes, atherosclerosis, stroke, Parkinson's disease and Alzheimer's disease; however, what remains to be seen is the important physiological roles for JNK. No data on efficacy of JNK inhibitors in inflammation in humans has been presented so

far (O'Neill, L. A. J. *Nature Reviews Drug Discovery* **2006**, specifically pages 5-6). Furhermore, it has not been established that this class of drugs (JNK inhibitors) can be used to treat immunological, neurodegenerative, or metabolic diseases. Therefore, support from the prior art is lacking, and it is essential that the specification provides for the lack of support in order for one of skill in the art to use these compounds as pharmaceuticals.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance provided which supports Applicant's claimed method for the *prevention* of any immunological, inflammatory, neurodegenerative, or metabolic diseases as indicated. The direction or guidance present in Applicants' Specification provides evidence that establishes the compounds of the present invention as inhibitors of JNK, see Test Examples 1 & 2; p. 587-590. Test Examples 3-8 on pages 591-594 demonstrate that the compounds described in formula (III) are involved in cell death, protecting against dopaminergic neuron degeneration, production of TNF-a, and the production of blood glucose. No *in vivo* data has been provided to support the scope of the instant claims.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 53-55, 59 & 60-62 are drawn to a compound according to Formula (III) for the treatment and/or prevention of immunological diseases, inflammatory diseases, neurodegenerative diseases, or metabolic diseases. In order to *prevent* a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, and then demonstrate that if the identified subject did not develop the disease, such an effect was the direct result of administration of the claimed invention. In order to treat a disease, one would need to demonstrate what the subject population is, what the necessary dose is for efficacy, and that the subject has recovered from such a disease.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20, 22, 23 and 50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over **Claims 20, 22, 23, and 50** of copending Application No. **10/447,948**. Although the conflicting claims are not identical, there is substantial overlap between said claims. Therefore, a reference or case of infringement that anticipates or renders obvious the claims of one application may also anticipate or render obvious the claims of the other application. Furthermore, both applications are drawn to compounds and compositions of the formula (III), which have been found useful for the inhibition of the JNK kinases. Therefore, one of ordinary skill in the art when faced with copending application **10/447,948** would be motivated to prepare applicants' instant elected invention as the conflicting claims generically encompass nearly 100% of the instantly claimed application for patent. The motivation would be to prepare additional compounds for the

inhibition of JNK kinases. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

Claim 23 is objected to because of the following informalities: the text is unclear in describing what is included within the limitations of the claim and what is excluded within the proviso. Appropriate correction is required. Examiner suggests an amendment such as: "provided that, when L is a single bond and X is a single bond then Y cannot be an optionally substituted C_{1-6} alkyl..."

Claims 50-52 are objected to as being dependent upon a rejected base **Claim 20**.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason M. Nolan, Ph.D.
Examiner
Art Unit 1626

Joseph K. M^{c}Kane
Supervisory Patent Examiner
Art Unit 1626
Date: March 12, 2007